RADIOPROTECTIVE ACTIVITY AND SYNTHESIS OF SILADITHIOACETALS AND GERMADITHIOACETALS DERIVED FROM N-SUBSTITUTED NAPHTHYLETHYLIMIDAZOLINE

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ABSTRACT

A number of organosilicon and organogermanium derivatives and some related compounds including the N-substituted 2-[1-naphthylmethyl]-2-imidazoline and 2-[1-(1-naphthyl)ethyl]-2-imidazoline have been prepared and the toxicity of some compounds have been determined in mice. In this paper we report the synthesis and the evaluation of the pharmacological activity of new organosilicon and organogermanium compounds such as sila- and germadithioacetals derived from N-substituted naphthylimidazoline.

INTRODUCTION

Recently, it has been reported that medetomidine [1] is a new imidazole drug that possesses selective and potent α_2-adrenergic properties. α_2-Adrenergic stimulation is known to mediate a variety of biological actions including hypertension, sedation, antianxiety, analgesia, hypothermia, decreased salivary secretions and mydriasis [2].

The selection of the naphthalene ring system was due to its presence in the potent α-adrenergic stimulant naphazoline. The presence of a methyl group attached at the benzylic position of medetomidine is important for optimal α_2-adrenergic activity [3].

Our group has already reported a considerable work in the field of the chemical radioprotection and pharmacological activity of organosilicon and organogermanium compounds [4-16]. Several organometallic classes derived from N-substituted naphthylmethylimidazoline showed a potent radioprotective activity.

Concerning the mechanism of the radioprotective activity of these compounds, it is well established that the main mechanisms of radioprotection are tissual oxygen tension decrease, free radical scavenging and hydrogen transfer [17]. However, the radioprotective action mechanism of naphthylmethylimidazoline remains unclear. Some recent and preliminary investigations seem to indicate that at least *in vitro*, it has no effect on lipidic peroxidation. Perhaps it acts through its vasoconstrictive effects, which can lower the tissual oxygen supply and hence decrease the radiation-induced lesions.

Another possible explanation of excellent activity of naphthylmethylimidazoline, the first non-sulfur radioprotective compound, is its evolution *in vivo* of the compound that forms anti-inflammatory products of naphthyl-1-acetic acid type [18]. Further studies are necessary to determine the precise mechanism of action.

Accordingly our objective, we have investigated a new series of organosilicon and organogermanium compounds derived from N-substituted 2-[1-(1-naphthyl)ethyl]-2-imidazoline.

Experimental section
General procedures

All manipulations were performed under an inert atmosphere of argon using standard Schlenck, glove box and high-vacuum-line techniques. All solvents used were freshly dried using standard techniques and all glassware was oven-dried. ^{1}H-NMR spectra were recorded on a Bruker AC 80 spectrometer operating at 80.13 MHz (chemical shifts are reported in parts per million relative to internal Me_4Si as reference) and ^{13}C-NMR spectra on an AC 200 spectrometer (50.32 MHz). The multiplicity of the ^{13}C-NMR signals was determined by the APT technique. Mass spectra under electron impact (EI) or chemical ionisation (CI/CH$_4$) conditions at 70 and 30 eV were obtained on Hewlett-Packard 5989 and Nermag R10-10H spectrometers. IR and UV spectra were recorded on Perkin-Elmer 1600 FT-IR and Lambda-17 spectrophotometers.

Table 1   Physicochemical data and analyses of derivatives 1-12

Cpd	Yield (%)	Physical properties and elemental analyses
1	87	$^1R = {}^2R = n\text{-}C_6H_{13}$; $^3R = CH_3$; M = Ge ^{1}H-NMR (CDCl$_3$): 0.88 (t, 6H, J = 5.6 Hz, C$\underline{H}_3$CH$_2$); 1.09 - 1.56 (m, 26H, (C$\underline{H}_2$)$_5$ and C$\underline{H}_3$-CHS); 1.70 (d, 6H, J = 6.8 Hz, C$\underline{H}_3$-CHS); 2.38 - 2.76 (m, 2H, CH$_3$-C$\underline{H}$S); 3.05 - 3.80 (m, 12H, C$\underline{H}_2$N); 4.47 (q, 2H, J = 6.8 Hz, C$\underline{H}$-CH$_3$); 7.12 - 7.50 (m, 8H, C$_{10}\underline{H}_7$); 7.63 - 7.95 (m, 4H, C$_{10}\underline{H}_7$); 8.09 - 8.35 (m, 2H, C$_{10}\underline{H}_7$). ^{13}C-NMR (CDCl$_3$): 14.12 (C$\underline{H}_3$CH$_2$); 19.07 (C$\underline{H}_3$-CH); 20.98 (C$\underline{H}_3$-CH); 21.09 (C$\underline{H}$-CH$_3$); 22.58 (C$\underline{H}_2$Ge); 23.41 (CH$_3$C$\underline{H}_2$); 24.69 (CH$_3$CH$_2$C$\underline{H}_2$); 31.10 (CH$_3$CH$_2$CH$_2$C$\underline{H}_2$); 31.49 (C$\underline{H}_2$CH$_2$Ge); 34.79 (C$\underline{H}$-CH$_3$); 50.28 (C$\underline{H}_2$N); 50.49 (C$\underline{H}_2$N); 52.69 (C$\underline{H}_2$N); 123.09 (aromatic C$\underline{H}$); 124.72 (arom. C$\underline{H}$); 125.61 (arom. C$\underline{H}$); 126.02 (arom. C$\underline{H}$); 126.18 (arom. C$\underline{H}$); 127.87 (arom. C$\underline{H}$); 129.21 (arom. C$\underline{H}$); 131.12 (arom. C$_{quat}$); 134.09 (arom. C$_{quat}$); 137.10 (arom. C$_{quat}$); 167.21 (N-C$\underline{\ }$=N). Analysis (C$_{48}$H$_{68}$N$_4$S$_2$Ge): Calcd. %: C, 68.85; H, 8.13; N, 6.69. Found %: C, 69.02; H, 8.17; N, 6.61.
2	89	$^1R = {}^2R = n\text{-}C_6H_{13}$; $^3R = H$; M = Ge ^{1}H-NMR (CDCl$_3$): 0.86 (t, 6H, J = 5.6 Hz, C$\underline{H}_3$CH$_2$); 1.02 - 1.47 (m, 20H, (C$\underline{H}_2$)$_5$); 1.68 (d, 6H, J = 6.9 Hz, C$\underline{H}_3$-CH); 2.36 - 2.84 (m, 4H, C$\underline{H}_2$S); 3.02 - 3.84 (m, 12H, C$\underline{H}_2$N); 4.43 (q, 2H, J = 6.9 Hz, C$\underline{H}$-CH$_3$); 7.21 - 7.62 (m, 8H, C$_{10}\underline{H}_7$); 7.68 - 7.93 (m, 4H, C$_{10}\underline{H}_7$); 8.08 - 8.19 (m, 2H, C$_{10}\underline{H}_7$). ^{13}C-NMR (CDCl$_3$): 14.22 (C$\underline{H}_3$CH$_2$); 19.13 (C$\underline{H}_3$-CH); 21.26 (C$\underline{H}_2$S); 22.70 (C$\underline{H}_2$Ge); 23.39 (CH$_3$C$\underline{H}_2$); 24.65 (CH$_3$CH$_2$C$\underline{H}_2$); 31.21 (CH$_3$CH$_2$CH$_2$C$\underline{H}_2$); 31.58 (C$\underline{H}_2$CH$_2$Ge); 34.89 (C$\underline{H}$-CH$_3$); 50.34 (C$\underline{H}_2$N); 50.61 (C$\underline{H}_2$N); 52.74 (C$\underline{H}_2$N); 123.17 (aromatic C$\underline{H}$); 124.86 (arom. C$\underline{H}$); 125.74 (arom. C$\underline{H}$); 126.12 (arom. C$\underline{H}$); 126.23 (arom. C$\underline{H}$); 127.93 (arom. C$\underline{H}$); 129.31 (arom. C$\underline{H}$); 131.23 (arom. C$_{quat}$); 134.14 (arom. C$_{quat}$); 137.18 (arom. C$_{quat}$); 167.36 (N-C$\underline{\ }$=N). Mass Spectrum: m/z 525 [M − 283]$^+$. Analysis (C$_{46}$H$_{64}$N$_4$S$_2$Ge): Calcd. %: C, 68.26; H, 7.91; N, 6.93. Found %: C, 68.33; H, 8.00; N, 7.05.
3	88	$^1R = {}^2R = i\text{-}C_5H_{11}$; $^3R = CH_3$; M = Ge ^{1}H-NMR (CDCl$_3$): 0.88 (d, 12H, J = 5.6 Hz, (C$\underline{H}_3$)$_2$CH); 1.05 - 1.49 (m, 16H, C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}$ and C$\underline{H}_3$CHS); 1.69 (d, 6H, J = 6.8 Hz, C$\underline{H}_3$-CH); 2.30 - 2.80 (m, 2H, C$\underline{H}$S); 3.06 - 3.88 (m, 12H, C$\underline{H}_2$N); 4.44 (q, 2H, J = 6.7 Hz, C$\underline{H}$-CH$_3$); 7.22 - 7.60 (m, 8H, C$_{10}\underline{H}_7$); 7.65 - 7.92 (m, 4H, C$_{10}\underline{H}_7$); 8.00 - 8.20 (m, 2H, C$_{10}\underline{H}_7$). ^{13}C-NMR (CDCl$_3$): 18.28 (C$\underline{H}_2$Ge); 19.10 (C$\underline{H}$S); 20.95 ((C$\underline{H}_3$)$_2$CH); 21.08 (C$\underline{H}_3$-CH); 22.09 (C$\underline{H}_3$-CH); 30.52 ((CH$_3$)$_2$C$\underline{H}$); 32.25 (C$\underline{H}_2$CH); 34.83 (C$\underline{H}$-CH$_3$); 50.26 (C$\underline{H}_2$N); 50.51 (C$\underline{H}_2$N); 52.65 (C$\underline{H}_2$N); 124.01 (aromatic C$\underline{H}$); 125.41 (arom. C$\underline{H}$); 125.73 (arom. C$\underline{H}$); 126.49 (arom. C$\underline{H}$); 126.64 (arom. C$\underline{H}$); 127.69 (arom. C$\underline{H}$); 128.66 (arom. C$\underline{H}$); 132.12 (arom. C$_{quat}$); 132.56 (arom. C$_{quat}$); 133.93 (arom. C$_{quat}$); 166.31 (N-C$\underline{\ }$=N). Analysis (C$_{46}$H$_{64}$N$_4$S$_2$Ge): Calcd. %: C, 68.26; H, 7.91; N, 6.93. Found %: C, 68.35; H, 7.94; N, 6.88.
4	91	$^1R = {}^2R = i\text{-}C_5H_{11}$; $^3R = H$; M = Ge ^{1}H-NMR (CDCl$_3$): 0.87 (d, 12H, J = 5.6 Hz, (C$\underline{H}_3$)$_2$CH); 1.06 - 1.44 (m, 10H, C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}$); 1.71 (d, 6H, J = 6.7 Hz, C$\underline{H}_3$-CH); 2.36 - 2.77 (m, 4H, C$\underline{H}_2$S); 3.07 - 3.79 (m, 12H, C$\underline{H}_2$N); 4.45 (q, 2H, J = 6.7 Hz, C$\underline{H}$-CH$_3$); 7.20 - 7.58 (m, 8H, C$_{10}\underline{H}_7$); 7.64 - 7.90 (m, 4H, C$_{10}\underline{H}_7$); 8.05 - 8.23 (m, 2H, C$_{10}\underline{H}_7$). ^{13}C-NMR (CDCl$_3$): 17.19 (C$\underline{H}_2$Ge); 18.28 (C$\underline{H}_2$S); 19.10 ((C$\underline{H}_3$)$_2$CH); 22.09 (C$\underline{H}_3$-CH); 30.52 ((CH$_3$)$_2$C$\underline{H}$); 32.25 (C$\underline{H}_2$CH); 34.83 (C$\underline{H}$-CH$_3$); 50.26 (C$\underline{H}_2$N); 50.51 (C$\underline{H}_2$N); 52.65 (C$\underline{H}_2$N); 124.01 (aromatic C$\underline{H}$); 125.41 (arom. C$\underline{H}$); 125.73 (arom. C$\underline{H}$); 126.49 (arom. C$\underline{H}$); 126.64 (arom. C$\underline{H}$); 127.69 (arom. C$\underline{H}$); 128.66 (arom. C$\underline{H}$); 132.12 (arom. C$_{quat}$); 132.56 (arom. C$_{quat}$); 133.93 (arom. C$_{quat}$); 166.31 (N-C$\underline{\ }$=N). Analysis (C$_{44}$H$_{60}$N$_4$S$_2$Ge): Calcd. %: C, 67.64; H, 7.69; N, 7.17. Found %: C, 67.82; H, 7.74; N, 7.09.
5	86	$^1R = p\text{-}CH_3\text{-}C_6H_4$; $^2R = CH_3$; $^3R = CH_3$; M = Ge ^{1}H-NMR (CDCl$_3$): 0.95 (s, 3H, C$\underline{H}_3$Ge); 1.35 (d, 6H, J = 6.7 Hz, C$\underline{H}_3$-CHS); 1.74 (d, 6H, J = 6.8 Hz, C$\underline{H}_3$-CH); 2.20-2.63 (m, 5H, p-C$\underline{H}_3$ and C$\underline{H}$S); 3.08-3.80 (m, 12 H, C$\underline{H}_2$N); 4.51 (q, 2H, J = 6.8 Hz, C$\underline{H}$-CH$_3$); 7.09-8.18 (m, 18 H, C$_6\underline{H}_4$ and C$_{10}\underline{H}_7$). ^{13}C-NMR (CDCl$_3$): 9.02 (C$\underline{H}_3$-Ge); 20.11 (p-C$\underline{H}_3$); 20.75 (C$\underline{H}_3$-CH); 21.21 (C$\underline{H}_3$-CH); 21.65 (C$\underline{H}$-CH$_3$); 34.22 (C$\underline{H}$-CH$_3$); 45.92 (C$\underline{H}_2$N); 46.40 (C$\underline{H}_2$N); 46.73 (C$\underline{H}_2$N); 123.20 (aromatic C$\underline{H}$); 125.74 (arom. C$\underline{H}$); 125.96 (arom. C$\underline{H}$); 128.41 (arom. C$\underline{H}$); 128.84 (arom. C$\underline{H}$); 129.39 (arom. C$\underline{H}$); 129.47 (arom. C$\underline{H}$); 129.70 (arom. C$\underline{H}$); 130.02 (arom. C$\underline{H}$); 131.79

(arom. C_{quat}); 132.26 (arom. C_{quat}); 136.21 (arom. C_{quat}); 140.29 (arom. C_{quat}); 146.49 (arom. C_{quat}); 170.93 (N-$\underline{C}$=N). Analysis ($C_{44}H_{52}N_4S_2Ge$): Calcd. %: C, 68.16; H, 6.71; N, 7.23. Found %: C, 68.22; H, 6.87; N, 7.19.

6   89 $^1R = p\text{-}CH_3\text{-}C_6H_4$; $^2R = CH_3$; $^3R = H$; M = Ge
^{1}H-NMR (CDCl$_3$): 0.99 (s, 3H, C$\underline{H}_3$Ge); 1.73 (d, 6H, J = 6.8 Hz, C$\underline{H}_3$-CH); 2.24-2.58 (m, 7H, p-C$\underline{H}_3$ and C$\underline{H}_2$S); 3.06-3.73 (m, 12 H, C$\underline{H}_2$N); 4.51 (q, 2H, J = 6.8 Hz, C$\underline{H}$-CH$_3$); 6.85-8.18 (m, 18 H, C$_6\underline{H}_4$ and C$_{10}\underline{H}_7$). ^{13}C-NMR (CDCl$_3$): 9.06 ($\underline{C}H_3$-Ge); 19.97 (p-$\underline{C}H_3$); 21.61 ($\underline{C}H_3$-CH); 29.70 ($\underline{C}H_2$S); 34.32 ($\underline{C}H$-CH$_3$); 45.84 ($\underline{C}H_2$N); 46.02 ($\underline{C}H_2$N); 47.26 ($\underline{C}H_2$N); 123.20 (aromatic $\underline{C}$H); 125.20 (arom. $\underline{C}$H); 125.78 (arom. $\underline{C}$H); 128.62 (arom. $\underline{C}$H); 128.89 (arom. $\underline{C}$H); 129.22 (arom. $\underline{C}$H); 129.36 (arom. $\underline{C}$H); 129.50 (arom. $\underline{C}$H); 132.23 (arom. $\underline{C}$H); 133.81 (arom. C_{quat}); 134.07 (arom. C_{quat}); 138.26 (arom. C_{quat}); 141.35 (arom. C_{quat}); 147.32 (arom. C_{quat}); 163.09 (N-$\underline{C}$=N). Analysis ($C_{42}H_{48}N_4S_2Ge$): Calcd. %: C, 67.51; H, 6.43; N, 7.50. Found %: C, 67.44; H, 6.48; N, 7.47.

7   87 $^1R = {}^2R = n\text{-}C_6H_{13}$; $^3R = CH_3$; M = Si
^{1}H-NMR (CDCl$_3$): 0.81 (t, 6H, J = 5.9 Hz, C$\underline{H}_3$CH$_2$); 1.01-1.44 (m, 26H, (C$\underline{H}_2$)$_5$ and C$\underline{H}_3$-CHS); 1.75 (d, 6H, J = 6.9 Hz, C$\underline{H}_3$-CH); 2.36-2.79 (m, 2H, CH$_3$-C$\underline{H}$S); 3.04-3.81 (m, 12H, C$\underline{H}_2$N); 4.53 (q, 2H, J = 6.9 Hz, C$\underline{H}$-CH$_3$); 7.25-7.56 (m, 8H, C$_{10}\underline{H}_7$); 7.61-7.86 (m, 4H, C$_{10}\underline{H}_7$); 7.90-8.21 (m, 2H, C$_{10}\underline{H}_7$). ^{13}C-NMR (CDCl$_3$): 14.12 ($\underline{C}H_3$CH$_2$); 16.18 ($\underline{C}H_2$Si); 18.48 (CH$_3\underline{C}H_2$); 18.67 ($\underline{C}H_3$CH); 19.58 ($\underline{C}HS$); 20.85 ($\underline{C}H_3$CH); 22.56 (CH$_3$CH$_2\underline{C}H_2$); 25.58 (CH$_3$CH$_2$CH$_2\underline{C}H_2$); 31.58 ($\underline{C}H_2$CH$_2$Si); 33.44 ($\underline{C}H$-CH$_3$); 44.40 ($\underline{C}H_2$N); 46.16 ($\underline{C}H_2$N); 50.13 ($\underline{C}H_2$N); 123.18 (aromatic $\underline{C}$H); 125.38 (arom. $\underline{C}$H); 125.79 (arom. $\underline{C}$H); 125.99 (arom. $\underline{C}$H); 127.02 (arom. $\underline{C}$H); 128.71 (arom. $\underline{C}$H); 128.87 (arom. $\underline{C}$H); 130.96 (arom. C_{quat}); 133.68 (arom. C_{quat}); 134.08 (arom. C_{quat}); 173.80 (N-$\underline{C}$=N). Mass Spectrum: m/z 792 [M]$^+$; 704 [M - 2×44]$^+$. Analysis ($C_{48}H_{68}N_4S_2Si$): Calcd. %: C, 72.73; H, 8.59; N, 7.07. Found %: C, 72.69; H, 8.65; N, 7.03.

8   92 $^1R = {}^2R = n\text{-}C_6H_{13}$; $^3R = H$; M = Si
^{1}H-NMR (CDCl$_3$): 0.83 (t, 6H, J = 5.7 Hz, C$\underline{H}_3$CH$_2$); 1.00-1.49 (m, 20H, (C$\underline{H}_2$)$_5$); 1.75 (d, 6H, J = 6.3 Hz, C$\underline{H}_3$-CH); 2.36-2.84 (m, 4H, C$\underline{H}_2$S); 2.95-4.10 (m, 12H, C$\underline{H}_2$N); 4.56 (q, 2H, J = 6.3 Hz, C$\underline{H}$-CH$_3$); 7.28-7.63 (m, 8H, C$_{10}\underline{H}_7$); 7.64-7.88 (m, 4H, C$_{10}\underline{H}_7$); 7.92-8.26 (m, 2H, C$_{10}\underline{H}_7$). ^{13}C-NMR (CDCl$_3$): 14.13 ($\underline{C}H_3$CH$_2$); 16.21 ($\underline{C}H_2$Si); 18.51 (CH$_3\underline{C}H_2$); 19.32 ($\underline{C}H_2$S); 22.59 ($\underline{C}H_3$-CH); 29.70 (CH$_3$CH$_2\underline{C}H_2$); 31.61 (CH$_3$CH$_2$CH$_2\underline{C}H_2$); 32.66 ($\underline{C}H_2$CH$_2$Si); 34.22 ($\underline{C}H$-CH$_3$); 46.02 ($\underline{C}H_2$N); 49.88 ($\underline{C}H_2$N); 49.99 ($\underline{C}H_2$N); 123.28 (aromatic $\underline{C}$H); 124.75 (arom. $\underline{C}$H); 125.39 (arom. $\underline{C}$H); 125.81 (arom. $\underline{C}$H); 126.50 (arom. $\underline{C}$H); 127.03 (arom. $\underline{C}$H); 128.87 (arom. $\underline{C}$H); 130.05 (arom. C_{quat}); 131.03 (arom. C_{quat}); 133.77 (arom. C_{quat}); 176.76 (N-$\underline{C}$=N). Analysis ($C_{46}H_{64}N_4S_2Si$): Calcd. %: C, 72.25; H, 8.38; N, 7.33. Found %: C, 72.29; H, 8.50; N, 7.14.

9   86 $^1R = {}^2R = i\text{-}C_5H_{11}$; $^3R = CH_3$; M = Si
^{1}H-NMR (CDCl$_3$): 0.86 (d, 12H, J = 5.6 Hz, (C$\underline{H}_3$)$_2$CH); 1.04 - 1.47 (m, 16H, C$\underline{H}_2$C$\underline{H}_2$CH and C$\underline{H}_3$CHS); 1.71 (d, 6H, J = 6.6 Hz, C$\underline{H}_3$-CH); 2.31 - 2.97 (m, 2H, C$\underline{H}$S); 3.13 - 3.84 (m, 12H, C$\underline{H}_2$N); 4.60 (q, 2H, J = 6.7 Hz, C$\underline{H}$-CH$_3$); 7.21 - 7.61 (m, 8H, C$_{10}\underline{H}_7$); 7.69 - 7.96 (m, 4H, C$_{10}\underline{H}_7$); 8.01 - 8.10 (m, 2H, C$_{10}\underline{H}_7$). ^{13}C-NMR (CDCl$_3$): 18.19 ($\underline{C}H_2$Si); 18.92 ($\underline{C}HS$); 21.15 (($\underline{C}H_3$)$_2$CH); 21.26 ($\underline{C}H_3$-CH); 22.15 ($\underline{C}H_3$-CH); 30.85 ((CH$_3$)$_2\underline{C}H$); 32.14 ($\underline{C}H_2$CH); 34.27 ($\underline{C}H$-CH$_3$); 50.69 ($\underline{C}H_2$N); 51.82 ($\underline{C}H_2$N); 53.44 ($\underline{C}H_2$N); 123.04 (aromatic $\underline{C}$H); 124.89 (arom. $\underline{C}$H); 125.70 (arom. $\underline{C}$H); 126.03 (arom. $\underline{C}$H); 126.56 (arom. $\underline{C}$H); 127.99 (arom. $\underline{C}$H); 128.39 (arom. $\underline{C}$H); 131.20 (arom. C_{quat}); 133.91 (arom. C_{quat}); 135.83 (arom. C_{quat}); 172.32 (N-$\underline{C}$=N). Analysis ($C_{46}H_{64}N_4S_2Si$): Calcd. %: C, 72.25; H, 8.38; N, 7.33. Found %: C, 72.17; H, 8.45; N, 7.29.

10   93 $^1R = {}^2R = i\text{-}C_5H_{11}$; $^3R = H$; M = Si
^{1}H-NMR (CDCl$_3$): 0.86 (d, 12H, J = 5.6 Hz, (C$\underline{H}_3$)$_2$CH); 1.07 - 1.46 (m, 10H, C$\underline{H}_2$C$\underline{H}_2$CH); 1.68 (d, 6H, J = 6.9 Hz, C$\underline{H}_3$-CH); 2.37 - 2.79 (m, 4H, C$\underline{H}_2$S); 3.13 - 3.81 (m, 12H, C$\underline{H}_2$N); 4.63 (q, 2H, J = 6.7 Hz, C$\underline{H}$-CH$_3$); 7.23 - 7.61 (m, 8H, C$_{10}\underline{H}_7$); 7.66 - 7.90 (m, 4H, C$_{10}\underline{H}_7$); 8.00 - 8.11 (m, 2H, C$_{10}\underline{H}_7$). ^{13}C-NMR (CDCl$_3$): 17.36 ($\underline{C}H_2$Si); 18.94 ($\underline{C}H_2$S); 20.31 (($\underline{C}H_3$)$_2$CH); 22.17 ($\underline{C}H_3$-CH); 30.86 ((CH$_3$)$_2\underline{C}H$); 32.37 ($\underline{C}H_2$CH); 34.36 ($\underline{C}H$-CH$_3$); 50.03 ($\underline{C}H_2$N); 50.24 ($\underline{C}H_2$N); 51.11 ($\underline{C}H_2$N); 123.81 (aromatic $\underline{C}$H); 124.95 (arom. $\underline{C}$H);

125.56 (arom. $\underline{C}$H); 126.34 (arom. $\underline{C}$H); 126.81 (arom. $\underline{C}$H); 127.74 (arom. $\underline{C}$H); 128.89 (arom. $\underline{C}$H); 131.29 (arom. C_{quat}); 133.93 (arom. C_{quat}); 136.53 (arom. C_{quat}); 171.81 (N-$\underline{C}$=N). Analysis ($C_{44}H_{60}N_4S_2Si$): Calcd. %: C, 71.74; H, 8.15; N, 7.61. Found %: C, 71.81; H, 8.19; N, 7.56.

11	87

$^1R = p\text{-}CH_3\text{-}C_6H_4$; $^2R = CH_3$; $^3R = CH_3$; M = Si
^{1}H-NMR (CDCl$_3$): 0.97 (s, 3H, C$\underline{H}_3$-Si); 1.38 (d, 6H, J = 6.8 Hz, C$\underline{H}_3$-CH-S); 1.71 (d, 6H, J = 6.9 Hz, C$\underline{H}_3$-CH); 2.23-2.56 (m, 5H, p-C$\underline{H}_3$ and C$\underline{H}$-S); 3.12-3.70 (m, 12 H, C$\underline{H}_2$N); 4.58 (q, 2H, J = 6.9 Hz, C$\underline{H}$-CH$_3$); 6.84-8.19 (m, 18 H, C$_6\underline{H}_4$ and C$_{10}\underline{H}_7$). ^{13}C-NMR (CDCl$_3$): 9.07 ($\underline{C}$H$_3$-Si); 18.84 (p-$\underline{C}$H$_3$); 19.64 ($\underline{C}$H$_3$-CH); 20.19 ($\underline{C}$H$_3$-CH); 21.64 ($\underline{C}$H-CH$_3$); 33.99 ($\underline{C}$H-CH$_3$); 44.51 ($\underline{C}$H$_2$N); 44.98 ($\underline{C}$H$_2$N); 46.29 ($\underline{C}$H$_2$N); 124.96 (aromatic $\underline{C}$H); 125.84 (arom. $\underline{C}$H); 126.02 (arom. $\underline{C}$H); 127.27 (arom. $\underline{C}$H); 127.69 (arom. $\underline{C}$H); 128.42 (arom. $\underline{C}$H); 129.06 (arom. $\underline{C}$H); 129.54 (arom. $\underline{C}$H); 133.16 (arom. $\underline{C}$H); 133.50 (arom. C_{quat}); 134.12 (arom. C_{quat}); 136.31 (arom. C_{quat}); 140.13 (arom. C_{quat}); 143.39 (arom. C_{quat}); 171.85 (N-$\underline{C}$=N). Analysis ($C_{44}H_{52}N_4S_2Si$): Calcd. %: C, 72.53; H, 7.14; N, 7.69. Found %: C, 72.47; H, 7.21; N, 7.76.

12	90

$^1R = p\text{-}CH_3\text{-}C_6H_4$; $^2R = CH_3$; $^3R = H$; M = Si
^{1}H-NMR (CDCl$_3$): 1.03 (s, 3H, C$\underline{H}_3$-Si); 1.72 (d, 6H, J = 7.1 Hz, C$\underline{H}_3$-CH); 2.24-2.60 (m, 7H, p-C$\underline{H}_3$ and C$\underline{H}_2$S); 3.08-3.66 (m, 12 H, C$\underline{H}_2$N); 4.51 (q, 2H, J = 7.1 Hz, C$\underline{H}$-CH$_3$); 6.85-8.11 (m, 18 H, C$_6\underline{H}_4$ and C$_{10}\underline{H}_7$). ^{13}C-NMR (CDCl$_3$): 8.88 ($\underline{C}$H$_3$-Si); 18.79 (p-$\underline{C}$H$_3$); 19.54 ($\underline{C}$H$_3$-CH); 22.61 ($\underline{C}$H$_2$S); 34.09 ($\underline{C}$H-CH$_3$); 44.96 ($\underline{C}$H$_2$N); 45.09 ($\underline{C}$H$_2$N); 46.13 ($\underline{C}$H$_2$N); 124.18 (aromatic $\underline{C}$H); 125.69 (arom. $\underline{C}$H); 126.19 (arom. $\underline{C}$H); 128.41 (arom. $\underline{C}$H); 129.12 (arom. $\underline{C}$H); 129.81 (arom. $\underline{C}$H); 130.79 (arom. $\underline{C}$H); 131.46 (arom. $\underline{C}$H); 133.18 (arom. $\underline{C}$H); 134.18 (arom. C_{quat}); 134.41 (arom. C_{quat}); 136.74 (arom. C_{quat}); 141.08 (arom. C_{quat}); 144.38 (arom. C_{quat}); 172.01 (N-$\underline{C}$=N). Analysis ($C_{42}H_{48}N_4S_2Si$): Calcd. %: C, 72.00; H, 6.86; N, 8.00. Found %: C, 72.11; H, 6.83; N, 8.06.

Melting points were taken uncorrected on a Leitz Biomed hot-plate microscope apparatus or, in capillary tubes, on a digital Electrothermal apparatus. Elemental analyses (C, H, N) were performed at the "Laboratoire de Microanalyse de l'Ecole Nationale Supérieure de Chimie" of Toulouse.

Synthesis of metalladithioacetals 1-12
All these compounds were prepared by a method already described.

Siladithioacetal 8 (method A)
To a stirred mixture of freshly distilled triethylamine (0.96 g, 9.5 mmol) and 1-(1-thioethyl)-2-[1-(1-naphthyl)ethyl]-2-imidazoline (2.70 g, 9.5 mmol) in 30 ml of THF was added dropwise with stirring a solution of diisoamyldichlorosilane (1.28 g, 4.75 mmol) in 30 ml of THF. The reaction mixture was refluxed under an argon atmosphere for 5 hours. After filtration, the residue was concentrated under vacuum to give **8** (3.2 g, 88 %).

Germadithioacetal 4 (method B)
A solution of bis(diethylamino)diisoamylgermane (1.71 g, 4.75 mmol) in 30 ml of THF was added slowly with stirring to a solution of 1-(1-thioethyl)-2-[1-(1-naphthyl)ethyl]-2-imidazoline (2.70 g, 9.5 mmol) in 30 ml of THF. The reaction mixture was refluxed under argon atmosphere for 5 hours. After cooling to room temperature, the volatile material was removed under vacuum to afford **4** (3.38 g, 91 %).

The physiochemical data and the analyses are reported in Table 1

Synthesis of selenodiazadihexylgermetane 13
Method C
To a solution of 1,3-bis(trimethylsilyl)selenourea (2.2 g, 8.23 mmol) in 100 ml of THF was added slowly with stirring a solution of bis(diethylamino)dihexylgermane (3.18 g, 8.23 mmol) in 10 ml of THF. The reaction mixture was refluxed for 5 hours. After the mixture was cooled to room temperature the volatiles were removed under vacuum to afford **13** (1.88 g, 45 %) as a yellow oil.

Method D
To a solution of 1,3-bis(trimethylsilyl)selenourea (2.2 g, 8.23 mmol) and triethylamine (1.67 g, 16.46 mmol) freshly distilled in 100 ml of THF was added dropwise with stirring a solution of dichlorodihexylgermane (2.58 g, 8.23 mmol) in 10 ml of THF. The reaction mixture was refluxed for 5 hours. After cooling to room temperature, the mixture was filtered and the volatiles were removed under vacuum to give **13** (1.59 g, 38 %).

13: ^{1}H-NMR (CDCl$_3$): 0.15 (s, 18H, (C$\underline{H}_3$)$_3$Si); 0.86 (t, 6H, J = 5.6 Hz, C$\underline{H}_3$CH$_2$); 1.10-1.50 (m, 20H, (C$\underline{H}_2$)$_5$). ^{13}C-NMR (CDCl$_3$): 1.06 (($\underline{C}$H$_3$)$_3$Si); 14.08 ($\underline{C}$H$_3$CH$_2$); 22.57 (CH$_3\underline{C}$H$_2$); 25.27 (CH$_3$CH$_2\underline{C}$H$_2$); 25.76 (CH$_3$CH$_2$CH$_2\underline{C}$H$_2$); 31.39 ($\underline{C}$H$_2$CH$_2$Ge); 32.13 ($\underline{C}$H$_2$Ge); C=Se not detected.

Mass spectrum: m/z 508 [M]$^+$; 431 [M - Se + 1]$^+$. Analysis ($C_{19}H_{44}N_2SeSi_2Ge$): Calcd. %: C, 44.79; H, 8.64; N, 5.50. Found %: C, 44.86; H, 8.69; N, 5.49.

Synthesis of selenodiazadiisoamylgermetane 14

Using the same experimental procedure as for the synthesis of **13**, the reaction of dichlorodiisoamylgermane (3.13 g, 10.96 mmol) in the presence of triethylamine (2.22 g, 21.92 mmol) or bis(diethylamino)diisoamylgermane (3.93 g, 10.96 mmol) with 1,3-bis(trimethylsilyl)selenourea (2.93 g, 10.96 mmol) does not lead to **14** but afford only the selenagermaadamantane **15** (2.50 g, 87 %) as a yellow solid, and 1,3-bis(trimethylsilyl)carbodiimide.

Synthesis of hexaselenatetrakis(isoamylgerma)adamantane 15

A solution of LiEt₃BH (57.20 mmol in 57.2 ml of THF) was added dropwise to elemental selenium (2.26 g, 28.60 mmol) via syringe. The mixture was stirred for 1 hour at room temperature. A solution of trichloroisoamylgermane (4.77 g, 19.07 mmol) in 25 ml of anhydrous THF was added at 0 °C for 1 hour. After the addition the reaction mixture was warmed to room temperature and stirred until the red colour of the selenium salt had disappeared (5 days). The solvent was removed *in vacuo* and the residue was extracted with toluene. After filtration and concentration the residue solid was crystallized from pentane to afford **15** (4.5 g, 90 %).

15: ^{1}H-NMR (CDCl₃): 0.90 (d, 24H, J = 5.4 Hz, (C$\underline{H}$₃)₂CH); 1.20-2.11 (m, 20H, C$\underline{H}$₂C$\underline{H}$₂C$\underline{H}$). ^{13}C-NMR (CDCl₃): 21.96 ($\underline{C}$H₃); 29.70 ($\underline{C}$H); 31.37 ($\underline{C}$H₂); 32.69 ($\underline{C}$H₂). Mass spectrum (CI: CH₄): m/z 1079 [M + 29]⁺. Analysis (C₂₀H₄₄Se₆Ge₄): Calcd. %: C, 22.90; H, 4.20. Found %: C, 22.93; H, 4.23.

This compound has been shown by X-Ray crystallographic methods to have an adamantane-type structure but the quality of crystal does not permit us to do a structure refinement.

Synthesis of 2-[1-(1-naphthyl)ethyl]-2-imidazoline 16

a) *N*-Boc 2-(1-naphthylmethyl)-2-imidazoline :

To a stirred solution of 2-(1-naphthylmethyl)-2-imidazoline (19 g, 90.35 mmol) in 200 ml of THF was added dropwise a solution of di*tert*butyldicarbonate (21 ml, 91.64 mmol) in 20 ml of THF. The mixture was stirred at room temperature for 8 hours. The volatiles were removed under vacuum to afford *N*-Boc 2-(1-naphthylmethyl)-2-imidazoline (25.52 g, 91 %).

^{1}H-NMR (CDCl₃): 1.35 (s, 9H, (C$\underline{H}$₃)₃C); 3.76 (s, 4H, C$\underline{H}$₂N); 4.49 (s, 2H, C$\underline{H}$₂-C₁₀H₇); 7.33-7.92 (m, 7H, C₁₀$\underline{H}$₇).

b) *N*-Boc 2-[1-(1-naphthyl)ethyl]-2-imidazoline :

To a stirred solution of *N*-Boc 2-(1-naphthylmethyl)-2-imidazoline (25.52 g, 82.22 mmol) in 300 ml of THF, at −78 °C, was added dropwise a solution of n-butyllithium 1.6 M in hexane (51.4 ml, 82.22 mmol). The mixture was stirred at this temperature for 3 hours. A solution of methyliodide (5.9 ml, 94.9 mmol) in 30 ml of THF was added dropwise. The mixture was then stirred at room temperature for a night. The volatiles were removed *in vacuo* and the residue was extracted with a mixture ether/pentane (1/1, 400 ml). After filtration, the solvent was removed under reduced pressure to afford *N*-Boc 2-[1-(1-naphthyl)ethyl]-2-imidazoline (23.86 g, 90 %).

^{1}H-NMR (CDCl₃): 0.99 (s, 9H, (C$\underline{H}$₃)₃C); 1.41 (d, 3H, J = 7.0 Hz, C$\underline{H}$₃-CH); 3.57 (s, 4H, C$\underline{H}$₂N); 5.15 (q, 1H, J = 7.0 Hz, C$\underline{H}$-CH₃); 7.20-7.90 (m, 7H, C₁₀$\underline{H}$₇). ^{13}C-NMR (CDCl₃): 19.09 ($\underline{C}$H₃-CH); 27.87 (($\underline{C}$H₃)₃-C); 35.80 ($\underline{C}$H-CH₃); 47.79 ($\underline{C}$H₂-N); 51.40 ($\underline{C}$H₂-N); 83.05 ((CH₃)₃-$\underline{C}$); 123.01 (aromatic $\underline{C}$H); 123.30 (arom. $\underline{C}$H); 125.64 (arom. $\underline{C}$H); 125.75 (arom. $\underline{C}$H); 126.36 (arom. $\underline{C}$H); 127.62 (arom. $\underline{C}$H); 128.80 (arom. $\underline{C}$H); 131.08 (arom. C$_{quat}$); 133.89 (arom. C$_{quat}$); 138.10 (arom. C$_{quat}$); 150.72 (arom. C$_{quat}$); 165.42 (N-$\underline{C}$=N). Mass spectrum: m/z 324 [M]⁺

c) 2-[1-(1-naphthyl)ethyl]-2-imidazoline :

To a stirred solution of *N*-Boc 2-[1-(1-naphthyl)ethyl]-2-imidazoline (23.86 g, 74.00 mmol) in 150 ml of acetic acid was added dropwise a solution of chlorhydric acid (10 ml, 36%). The mixture was stirred at 40 °C for 5 hours. The mixture was diluted with 400 ml of water and the aqueous layer was extracted with dichloromethane (4×150 ml). The organic layer was washed with a solution of NaOH (25 %). The organic layer was then dried over Na₂SO₄. Evaporation of solvent *in vacuo* gave **16** (8.63 g, 52 %). mp: 160-161 °C.

16: ^{1}H-NMR (CDCl₃): 1.70 (d, 3H, J = 7.1 Hz, C$\underline{H}$₃-CH); 3.53 (s, 4H, C$\underline{H}$₂N); 4.39 (q, 1H, J = 7.1 Hz, C$\underline{H}$-CH₃); 7.09 (s, 1H, N$\underline{H}$); 7.40-7.61 (m, 4H, C₁₀$\underline{H}$₇); 7.60-7.81 (m, 2H, C₁₀$\underline{H}$₇); 7.82-8.15 (m, 1H, C₁₀$\underline{H}$₇). ^{13}C-NMR (CDCl₃): 18.95 ($\underline{C}$H₃-CH); 35.50 ($\underline{C}$H-CH₃); 47.76 ($\underline{C}$H₂-N); 123.08 (arom. $\underline{C}$H); 124.61 (arom. $\underline{C}$H); 125.63 (arom. $\underline{C}$H); 125.96 (arom. $\underline{C}$H); 126.67 (arom. $\underline{C}$H); 128.13 (arom. $\underline{C}$H); 129.00 (arom. $\underline{C}$H 131.24 (arom. C$_{quat}$); 133.87 (arom. C$_{quat}$); 136.71 (arom. C$_{quat}$); 171.80 (N-$\underline{C}$=N). I.R. (cm⁻¹): ν$_{NH}$ = 3430. Mass spectrum: m/z 223 [M-1]⁺. Analysis (C₁₅H₁₆N₂): Calcd. %: C, 80.36; H, 7.14; N, 12.50. Found %: C, 80.70; H, 7.21; N, 12.09.

Synthesis of 1-(1-thioethyl)-2-[1-(1-naphthyl)ethyl]-2-imidazoline 17

A solution of 2-[1-(1-naphthyl)ethyl]-2-imidazoline **16** (3.66 g, 16.32 mmol) in 60 ml of dry toluene was mixed with a solution of ethylene sulfide (1.15 ml, 19.58 mmol) in 20 ml of dry toluene (sealed tube, argon flushed). The reaction mixture was then heated (110 °C oven) for 22 hours. After cooling, 100 ml of cold diethyl ether was added with stirring to the reaction mixture and a small amount of polyethylene sulfide was filtered. The solvent was removed under reduced pressure to give a yellow pasty product **17** (3.25 g, 70 %).

17: ^{1}H-NMR (CDCl₃): 1.68 (d, 3H, J = 6.8 Hz, C$\underline{H}$₃-CH); 2.43 (s, 1H, S$\underline{H}$); 2.54-2.84 (m, 2H, C$\underline{H}$₂-S); 3.02-3.91 (m, 6H, C$\underline{H}$₂N); 4.41 (q, 1H, J = 6.8 Hz, C$\underline{H}$-CH₃); 7.38-7.50 (m, 4H, C₁₀$\underline{H}$₇); 7.58-7.79 (m, 2H,

$C_{10}\underline{H}_7$); 7.80-8.13 (m, 1H, $C_{10}\underline{H}_7$). ^{13}C-NMR (CDCl$_3$): 19.09 ($\underline{C}H_3$-CH); 23.40 ($\underline{C}H_2$-S); 35.12 ($\underline{C}H$-CH$_3$); 48.85 ($\underline{C}H_2$-N); 49.09 ($\underline{C}H_2$-N); 52.41 ($\underline{C}H_2$-N); 122.81 (arom. $\underline{C}$H); 124.54 (arom. $\underline{C}$H); 125.43 (arom. $\underline{C}$H); 125.80 (arom. $\underline{C}$H); 126.09 (arom. $\underline{C}$H); 127.78 (arom. $\underline{C}$H); 129.12 (arom. $\underline{C}$H); 131.04 (arom. C$_{quat}$); 133.85 (arom. C$_{quat}$); 136.67 (arom. C$_{quat}$); 168.36 (N-$\underline{C}$=N). I.R. (cm^{-1}): ν_{SH} = 2542. Mass spectrum: m/z 283 [M-1]$^+$. Analysis (C$_{17}$H$_{20}$N$_2$S): Calcd. %: C, 71.83; H, 7.04; N, 9.86. Found %: C, 71.89; H, 7.17; N, 9.77.

Synthesis of 1-(2-thiopropyl)-2-[1-(1-naphthyl)ethyl]imidazoline 18

Using the same experimental procedure as for the synthesis of **17**, the reaction of **16** (3.66 g, 16.32 mmol) with propylene sulfide (1.29 ml, 16.40 mmol) leads to a yellow pasty product **18** (3.17 g, 65 %).

18: ^{1}H-NMR (CDCl$_3$): 1.24 (d, 3H, J = 6.6 Hz, C$\underline{H}_3$-CH); 1.65 (d, 3H, J = 6.9 Hz, C$\underline{H}_3$-CH); 2.48 (s, 1H, S$\underline{H}$); 2.58-2.86 (m, 1H, C$\underline{H}$-CH$_3$); 3.06-4.02 (m, 6H, C$\underline{H}_2$N); 4.46 (q, 1H, J = 6.9 Hz, C$\underline{H}$-CH$_3$); 7.11-7.52 (m, 4H, C$_{10}\underline{H}_7$); 7.66-7.82 (m, 2H, C$_{10}\underline{H}_7$); 7.84-8.16 (m, 1H, C$_{10}\underline{H}_7$). ^{13}C-NMR (CDCl$_3$): 19.13 ($\underline{C}H_3$-CH); 21.75 ($\underline{C}H$-CH$_3$); 23.08 ($\underline{C}H_3$-CH); 35.17 ($\underline{C}H$-CH$_3$); 48.89 ($\underline{C}H_2$-N); 49.21 ($\underline{C}H_2$-N); 52.46 ($\underline{C}H_2$-N); 123.01 (arom. $\underline{C}$H); 124.61 (arom. $\underline{C}$H); 125.51 (arom. $\underline{C}$H); 125.90 (arom. $\underline{C}$H); 126.13 (arom. $\underline{C}$H); 127.83 (arom. $\underline{C}$H); 129.19 (arom. $\underline{C}$H); 131.09 (arom. C$_{quat}$); 134.06 (arom. C$_{quat}$); 137.02 (arom. C$_{quat}$); 168.61 (N-$\underline{C}$=N). I.R. (cm^{-1}): ν_{SH} = 2548. Mass spectrum: m/z 297 [M-1]$^+$. Analysis (C$_{18}$H$_{22}$N$_2$S): Calcd. %: C, 72.48; H, 7.38; N, 9.40. Found %: C, 72.57; H, 7.61; N, 9.32.

Synthesis of 1, 3-bis(trimethylsilyl)selenourea 19

To a stirred solution of selenourea (10 g, 81.29 mmol) and triethylamine (36 ml, 186.96 mmol) in 200 ml of THF was added dropwise a solution of chlorotrimethylsilane (20.6 ml, 81.29 mmol) in 50 ml of THF. The reaction mixture was refluxed under an argon atmosphere for 8 hours. After filtration, the residue was concentrated *in vacuo* to afford **19** (18.47 g, 85 %). mp: 146-148 °C (dec.).

19: ^{1}H-NMR (CDCl$_3$): 0.35 (s, 18H, (C$\underline{H}_3$)$_3$Si); 6.20 (s, 2H, N$\underline{H}$). ^{13}C-NMR (CDCl$_3$): 1.02 (($\underline{C}H_3$)$_3$Si); C=Se not detected. Mass spectrum: m/z 267 [M]$^+$. Analysis (C$_7$H$_{20}$N$_2$SeSi$_2$): Calcd. %: C, 31.34; H, 7.46; N, 10.45. Found %: C, 31.41; H, 7.51; N, 10.41.

Pharmacology: evaluation of radioprotection

Three- month-old male mice (Swiss, France), 25 g body weight, were used.

The radioprotective effect of compounds was evaluated by determining the dose reduction factor (DRF), defined as the ratio of 50% lethal-dose irradiation 30 days (LD$_{50}$/30 days) of injected mice to that of control mice. Initially the survival rate was determined 30 days after irradiation in different groups of 10 mice receiving an intraperitoneal (i.p.) injection of the test compound with a dose equal to half or one-eighth of its LD$_{50}$ 15 or 90 min before whole-body irradiation delivered with a dose equal to the LD$_{100}$/30 days of control mice (7.5, 7.75 or 8 Gy according to the irradiation date), or with a dose equal to this dose + 2 Gy. When necessary, other irradiation doses were tested in order to evaluate the irradiation LD$_{50}$ of protected mice by the Kraber method (calculated or graphic). [19]

The radiosensitivity of the strain was regularly monitored by the determination of lethality curves of males and females. The LD$_{50}$/30 days was between 6.5 ± 0.3 and 6.75 ± 0.3 Gy according to the date (P < 0.05). Under these conditions significant protection was observed with a DRF value superior to 1.15.

The toxicity was evaluated by a Probit analysis of the LD$_{50}$, [20-21] the dose range being determined in a preliminary study. Five groups of ten mice were then injected with different doses within this range.

RESULTS AND DISCUSSION

Synthesis of metalladithioacetals ^{1}R^{2}RM[SCH(^{3}R)CH$_2$–NEI]$_2$

NEI = 2-[1-(1-naphthyl)ethyl]-2-imidazoline

The synthesis of sila- and germadithioacetals compounds derived from *N*-substituted 2-[1-(1-naphthyl)ethyl]-2-imidazoline was realised by two methods, A and B [4, 22].
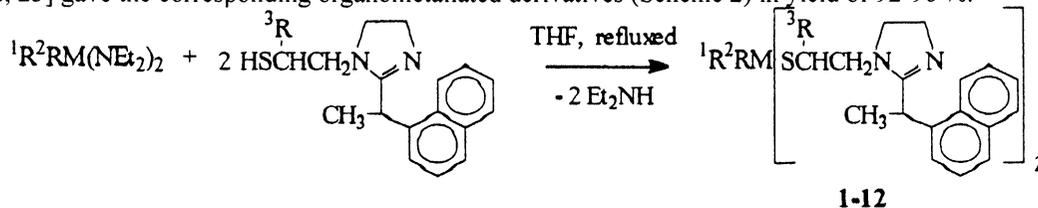
Method A

The action of the dichlorodiorganometallane [22] on two equivalents of *N*-substituted naphthylimidazoline in refluxing anhydrous tetrahydrofuran in the presence of freshly distilled triethylamine gave the acyclic derivatives (Scheme 1) in yields of 85-90 %.
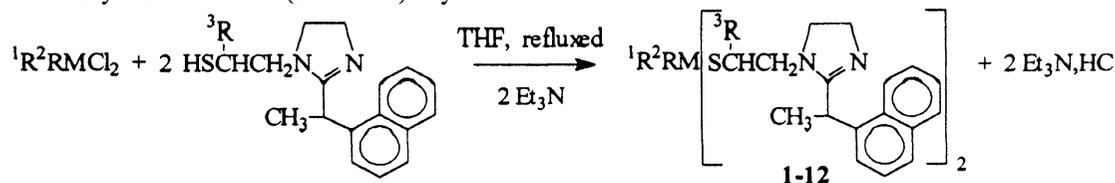
Scheme 1

Method B

The reaction of two equivalents of *N*-substituted naphthylimidazoline with the bis(diethylamino)dialkylmetallane in anhydrous tetrahydrofuran (a cleavage of M-N bonds by the SH groups) [4, 22, 23] gave the corresponding organometallated derivatives (Scheme 2) in yield of 92-96 %.

$$^1R^2RM(NEt_2)_2 \ + \ 2 \ HSCHCH_2N{\Longrightarrow}N \quad \xrightarrow[- \ 2 \ Et_2NH]{THF, \ refluxed} \quad ^1R^2RM\left[SCHCH_2N{\Longrightarrow}N\right]_2$$

1-12

Scheme 2

M = Ge		M = Si	
$^1R = {}^2R = $ n-C_6H_{13}; $^3R = CH_3$	(1)	$^1R = {}^2R = $ n-C_6H_{13}; $^3R = CH_3$	(7)
$^1R = {}^2R = $ n-C_6H_{13}; $^3R = H$	(2)	$^1R = {}^2R = $ n-C_6H_{13}; $^3R = H$	(8)
$^1R = {}^2R = $ *i*-C_5H_{11}; $^3R = CH_3$	(3)	$^1R = {}^2R = $ *i*-C_5H_{11}; $^3R = CH_3$	(9)
$^1R = {}^2R = $ *i*-C_5H_{11}; $^3R = H$	(4)	$^1R = {}^2R = $ *i*-C_5H_{11}; $^3R = H$	(10)
$^1R = $ p-CH_3-C_6H_4, $^2R = CH_3$; $^3R = CH_3$	(5)	$^1R = $ p-CH_3-C_6H_4, $^2R = CH_3$; $^3R = CH_3$	(11)
$^1R = $ p-CH_3-C_6H_4, $^2R = CH_3$; $^3R = H$	(6)	$^1R = $ p-CH_3-C_6H_4, $^2R = CH_3$; $^3R = H$	(12)

Synthesis of selenodiazagermetane R_2Ge-$N(SiMe_3)(C=Se)N(SiMe_3)$

- Case R = n-C_6H_{13} :

This compound was also synthesised by two methods, C and D.

Method C

Treatment of 1,3-bis(trimethylsilyl)selenourea, in stoichiometric amounts, with bis(diethylamino)dihexylgermane in refluxing anhydrous tetrahydrofuran resulted with a cleavage of Ge-N bonds by the NH groups (a transamination reaction) [22-26] forming the corresponding diazagermetane (Scheme 3) in yield of 45 %.

$$(n\text{-}C_6H_{13})_2Ge(NEt_2)_2 \ + \ Me_3Si(H)N-\underset{\underset{Se}{\|}}{C}-N(H)SiMe_3 \quad \xrightarrow[- \ 2 \ Et_2NH]{THF, \ refluxed} \quad (n\text{-}C_6H_{13})_2Ge\underset{\underset{Me_3Si}{\overset{Me_3Si}{N}}}{\overset{N}{<}}C=Se$$
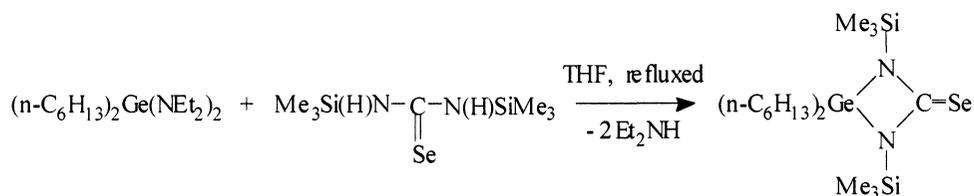
Scheme 3

Method D

The action of dichlorodihexylgermane, in stoichiometric amounts, on 1,3-bis(trimethylsilyl)selenourea, in refluxing anhydrous tetrahydrofuran in the presence of freshly distilled triethylamine gave by a cyclization reaction, with elimination of hydrochloric acid from Ge-Cl and NH [22,26] group, the corresponding product (Scheme 4) in yield of 38 %.

$$(n\text{-}C_6H_{13})_2GeCl_2 \ + \ Me_3Si(H)N-\underset{\underset{Se}{\|}}{C}-N(H)SiMe_3 \quad \xrightarrow[- \ 2 \ Et_3N,HCl]{THF, \ Et_3N} \quad (n\text{-}C_6H_{13})_2Ge\underset{\underset{Me_3Si}{\overset{Me_3Si}{N}}}{\overset{N}{<}}C=Se$$

13
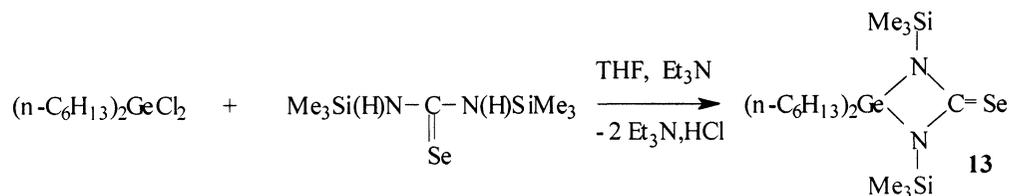
Scheme 4

- Case R = *i*-C_5H_{11} :

Using the same procedures described above, the reaction between bis(diethyl-amino)diisoamylgermane or dichlorodiisoamylgermane and 1,3-bis(trimethylsilyl)selenourea does not lead to stable heterocycle but gives only the selenagermaadamantane **15** and 1,3-bis(trimethylsilyl)carbodiimide probably via the intermediate selenodiazagermetane. (Scheme 5).
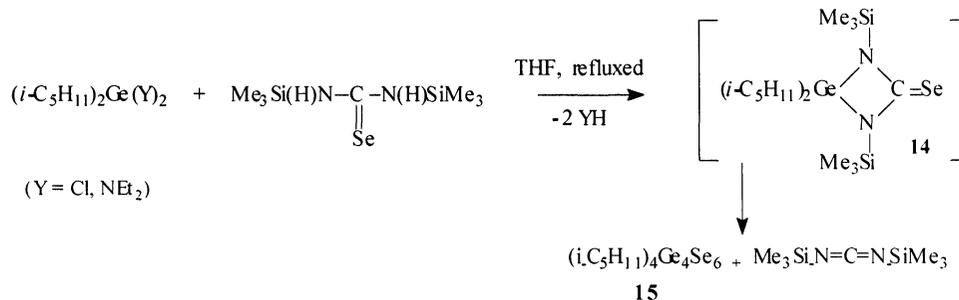
Scheme 5
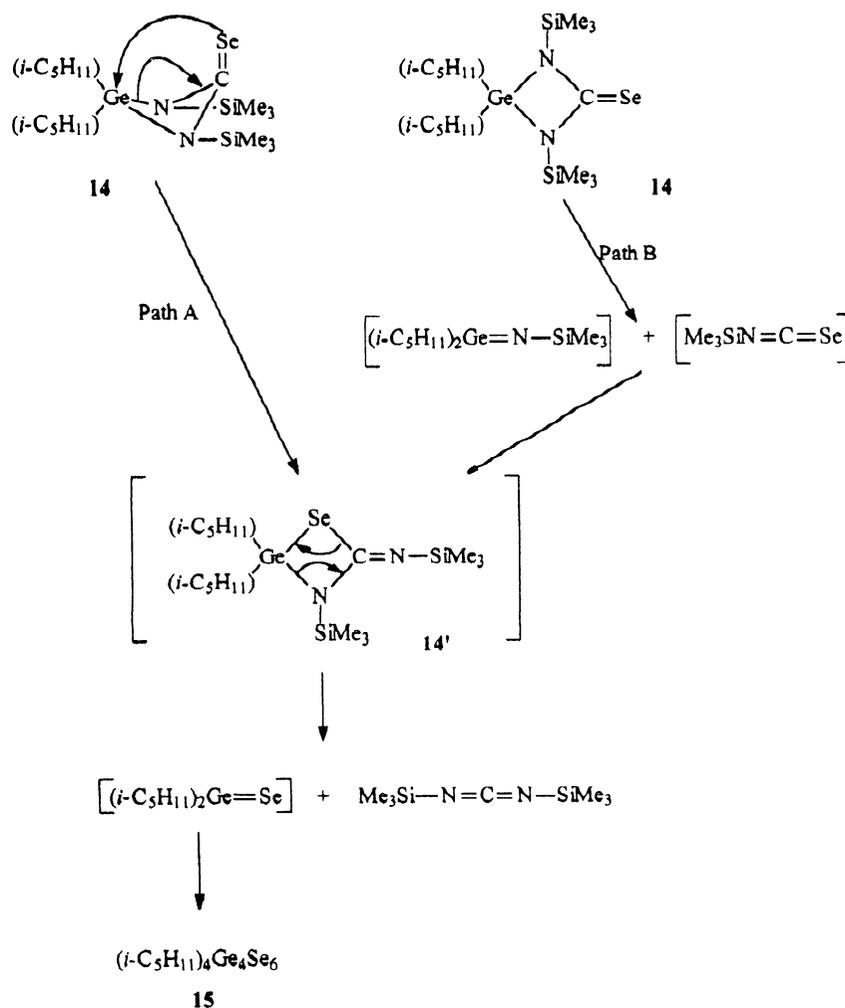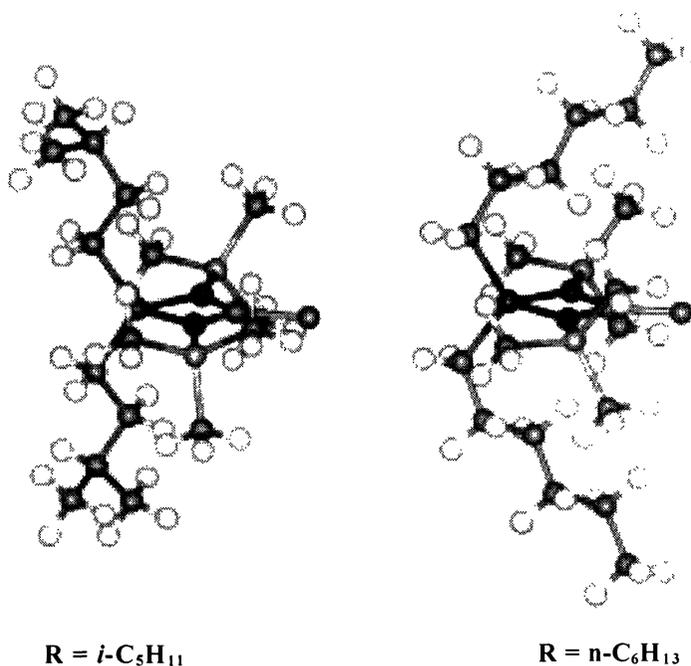

Scheme 6

Reaction mechanism

The formation of the selenagermaadamantane may be explained by two ways as follows (Scheme 6).

-    Path A: The nucleophilic intramolecular attack of selenium on the germanium atom leads to a corresponding intermediate **14'**. Then, this cyclic intermediate **14'** undergoes a decomposition to give the germaneselone and 1,3-bis(trimethylsilyl)carbodiimide.
-    Path B: The ring cleavage of **14** results in the formation of the monomeric species [(*i*-C_5H_{11})$_2$Ge=N-SiMe$_3$] and [Me$_3$Si-N=C=Se] as an intermediate, which submits to a pseudo Wittig reaction to afford the intermediate **14'**.

The germaneselone derivative showed a rearrangement to give preferentially the selenagermaadamantane **15** which has been completely characterised by usual spectroscopies, mass spectrometry and X-ray diffraction structure.

Molecular modelisation study (ESSF field)

This study showed the very important steric bulk of the isoamyl groups. The heterocycle **13** seems to benefit a protection of the reactive centre induced by the hexyl groups.

R = *i*-C$_5$H$_{11}$ R = n-C$_6$H$_{13}$

Synthesis of selenagermaadamantane 15

The treatment of isoamyltrichlorogermane with lithium selenide gave tetragermahexaselenide **15** [27]. (Scheme 7). The structure was determined by X-ray crystallography.

4 (*i*-C$_5$H$_{11}$)GeCl$_3$ +   6 Li$_2$Se $\xrightarrow[\text{refluxed}]{\text{THF}}$

15
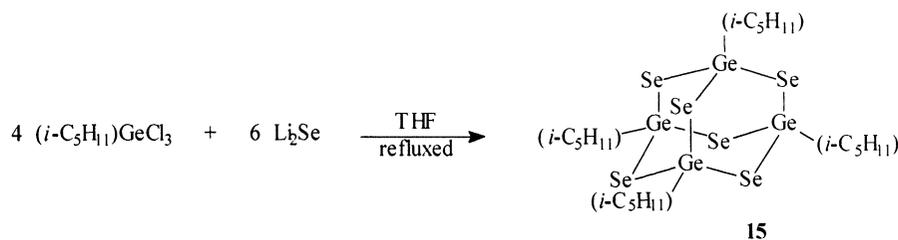
Scheme 7

Synthesis of the 2-[1-(1-naphthyl)ethyl]-2-imidazoline 16

This product was synthesised according to the following reaction scheme. (Scheme 8).

Scheme 8
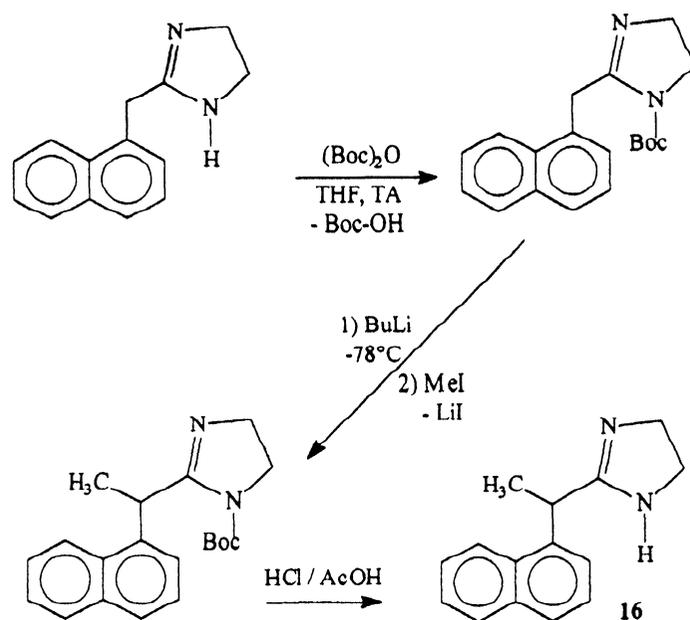
Synthesis of 17 and 18

The stoichiometric addition of thiirane or methylthiirane to **16** in toluene at 110 °C leads respectively to 1-(1-thioethyl)-2-[1-(1-naphthyl)ethyl]-2-imidazoline **17** and 1-(2-thiopropyl)-2-[1-(1-naphthyl)ethyl]-2-imidazoline **18** (i.e. by a cleavage of the C-S bond by the NH group [28]) (Scheme 9) in yields of 70 and 65%.

R = H   **17**
R = Me   **18**
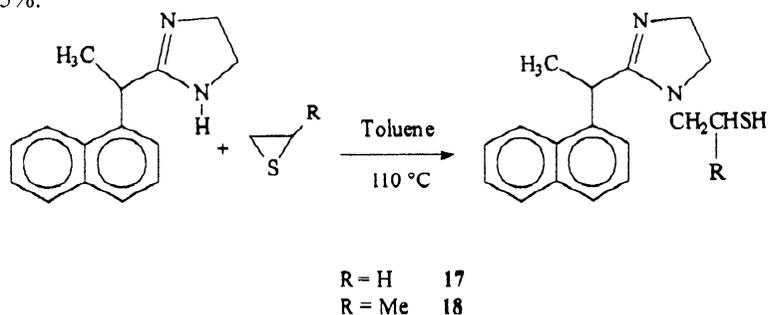
Scheme 9

Synthesis of 1,3-bis(trimethylsilyl)selenourea 19

The reaction between equimolar amounts of selenourea and chlorotrimethylsilane in the presence of triethylamine in anhydrous refluxing tetrahydrofuran gives **19** (Scheme 10) in yield of 85 %.

$$H_2N-\underset{\underset{Se}{\|}}{C}-NH_2 \quad + \quad 2\,Me_3SiCl \quad \xrightarrow{\ THF\ /\ 2\ Et_3N\ } \quad Me_3Si(H)N-\underset{\underset{Se}{\|}}{C}-N(H)SiMe_3 \quad + \quad 2\,Et_3N,HCl$$

19
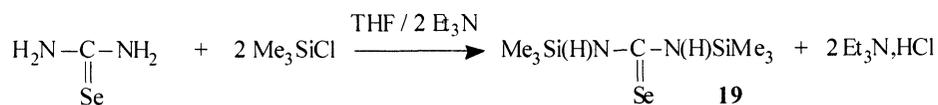
Scheme 10

Table 2   Toxicity in mice of some organic and organometallic derivatives

Compound	LD$_{50}$ (mg/kg) (mmol/kg)
	106 0.473
	50 0.238
	80 0.106
	212 0.271
	185 0.221
	150 0.192
Me$_3$Si(H)N—C—N(H)SiMe$_3$ ‖ Se	> 75 0.281
	> 600 1.180

Evaluation of the toxicity

The toxicity obtained with the different compounds has been summarized in table 2. The biological protocol has been detailed in the *Experimental section*.

The 2-[1-(1-naphthyl)ethyl]-2-imidazoline (NEI) compounds seems to be less toxic than their 2-(1-naphthylmethyl)-2-imidazoline (NMI) homologous. For example, NEI (16) show a two times lower molar toxicity than NMI. The lower toxicity of organometallic compounds compared with basic materials is confirmed by comparison between the toxicity of 13 and 19. Indeed compound 13 is eight times less toxic (LD$_{50}$ > 600 mg/Kg) than the starting derivative 19 (LD$_{50}$ > 75 mg/Kg). This means that the organogermanium compound 13 have a toxicity four times lower than 19 one (expressed in mol fractions).

The results of the radioprotective activity will be reported at a later date.

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